PROGNOSTICATION OF NEWBORNS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY WITH EEG AND IMAGING STUDIES

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PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH

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DECLARATION

I hereby declare that this dissertation entitled **PROGNOSTICATION OF NEWBORNS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY WITH EEG AND IMAGING STUDIES.** was prepared by me under the guidance and supervision of Professor Sarah Paul, DCH, MD, PSG Institute of Medical Sciences and Research, Coimbatore.

The dissertation is submitted to the Tamilnadu Dr.MGR Medical University in fulfillment of the University regulation for the award of MD degree in pediatrics. This dissertation has not been submitted for the award of any other Degree or Diploma

Dr Annu Jose

CERTIFICATE BY THE GUIDE

This is to certify that the thesis entitled " **PROGNOSTICATION OF NEWBORNS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY WITH EEG AND IMAGING STUDIES"** is the bonafide work of Dr. Annu Jose done under my guidance and supervision in the department of Pediatrics, PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations of Dr.MGR Medical university for the award of MD degree in Pediatrics

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Master chart

Key to Master Chart

Introduction

At the dawn of the third millennium, HIE remains the most common neurological disease of the perinatal period across all gestational ages. Many prospective and retrospective studies have been done attempting to link the various neurologic abnormalities to specific disorders of gestation or the perinatal period. Pathologic studies of the brain have produced careful descriptions of various cerebral abnormalities in patients with non progressive neurologic disorders and have led to attempts, often highly speculative, to formulate their causes.

Early recognition of the severity of the condition is crucial in predicting the probable neurological outcome as well as for deciding the need for stimulation therapy for the physico-psycho-social development of the infant.

In this study an attempt has been made to correlate electroencephalogram, CT and MRI brain done in early infancy with the neurological outcome of term asphyxiated newborns.

Review of literature

More than 160 years has elapsed since the publication of Little's classic paper linking abnormal parturition, difficult labor, premature birth, and asphyxia neonatorum with spastic rigidity of the limbs , [1] the pathogenesis of cerebral birth injuries is still an enigma and not completely understood.

The pendulum has swung from the long held belief that nearly all 'cerebral palsy' resulted from birth asphyxia – to the other extreme, that HIE is responsible for only a minority of cases , as many other genetic and acquired causes of this syndrome have been recognized. But still HIE is among the most important causes of long term neurological handicap dating from the perinatal period. [2]

Perinatal asphyxia producing hypoxic ischemic encephalopathy occur in 6 in 1000 live birth and in an even higher percentage of low-birth-weight infants. Perinatal asphyxia is a result of disturbed exchange of oxygen and carbondioxide and it can produce hypoxic ischemic encephalopathy as a result of deprivation of oxygen to the brain by hypoxemia (the reduction in oxygen in the blood), ischemia (decreased blood flow to and within the brain), or both. [3]

Historical aspects

William John Little (1810-1894) an orthopaedic surgeon from London was the first to describe a case of spastic diplegia. He wrote articles which linked ‘abnormal parturition, difficult labour prematurity and asphyxia’ with intellectual impairment and neurological deficit later in life .This later on lead to a lot of debate and confusion regarding the etiology and classification of cerebral palsy in children. [4, 5]

Later Sir William Osler published ‘The Cerebral Palsies of Children’. He was the first to refer the consequence of HIE as a nonprogressive neuromuscular disease in children. [6] Sigmund Freud , before he became a proclaimed psychiatrist had published several papers on spastic diplegia in children and was of the opinion that difficult delivery and birth trauma can lead to neurologic problems in children but there might also be some other underlying problem in the developing brain which had caused the problem at birth [7]

Incidence

Hypoxic-ischemic encephalopathy (HIE) of the newborn occurs with the incidence of 1–4/1000. [8] Between 20 % and 50 % of newborn infants affected by perinatal brain injury die during the newborn period, and 25–60 % of the survivors suffer from permanent neuro developmental handicaps, including cerebral palsy, seizures, mental retardation, and learning disabilities. [8-10]

The rate is approximately 10 times higher in the lower socio-economic areas, accounting for one million intrapartum-related deaths per year. [11, 12]

Criteria's for diagnosing intrapartal asphyxia as a cause of brain injury

AAP/ACOG (1996)(13)	International CerebralPalsy Task Force (1999)(14)	AAP/ACOG (2002)(15)
pH<7.0	pH<7.0;BD≥12mmol/L (neonatal blood sampling)	pH<7.0;BD≥12mmol/L (Umbilical or neonantal blood sampling)
APGAR≤ 3@5 min	APGAR<6@5 min	APGAR≤ 3@5 min
	Sentinel event/Abrupt fetal heart rate change	Sentinel event/Abrupt fetal heart rate change
Neonatal Encephalopathy	Encephalopathy II-III	Encephalopathy II-III
Multi-organ dysfunction	Multi-organ failure	Multi-organ failure within 72 hours
	Cerebral Palsy	Cerebral Palsy and exclusion of other causes of brain injury
	Imaging evidence	Imaging evidence

Perinatal asphyxia can also be defined by the presence of two or more of the following [16]

a) Signs of fetal distress as indicated by one or more of the following:
   - Fetal bradycardia (≤ 100 beats/min)
   - Thick meconium staining of liquor
   - Abnormal cardiotocography recordings.
   - Arterial cord pH < 7.2 or base deficit > 15mmol/L

b) Apgar score < 6 at five minutes of life.

c) Need for > 1 minute of positive pressure ventilation before occurrence of sustained respiration

Etiopathogenesis of hypoxic ischemic encephalopathy

The central defect that leads to brain injury in hypoxic ischemic encephalopathy is a decrease in oxygen supply to the brain. This could occur as a result of reduced amount of oxygen in the blood (hypoxia) or a reduced supply of blood to the brain (ischemia).Hypoxia or ischemia, either alone or both together can occur during the perinatal period as a consequence of asphyxia leading to the subsequent brain injury or damage.

During the course of normal labour and child birth most of the babies are born with a little reduced oxygen reserve. This mild depletion of oxygen occurs as a

combined effect of various physiological alterations taking place during child birth. These include [17]

a) A reduction in blood flow to the placenta due to uterine contractions, intermittent cord compression, maternal dehydration, and maternal alkalosis due to hyperventilation
b) A reduction in oxygen supply to the fetus as a result of the decreased placental blood flow
c) Increased oxygen consumption in both the mother and the fetus due to the physiological stress.

This very meager hypoxia is usually well tolerated by the fetus or newborn. But added to this physiological stress when there is some amount of perinatal asphyxia there occurs major intracellular and metabolic disturbances which results in pathological hypoxic ischemic injury.

Hypoxia

Hypoxia/asphyxia is generally assumed to be the "cause" of brain damage. Babies who develop HIE are usually born "asphyxiated", and ACOG [18] "strongly supports the concept that a neonate who had hypoxia prior to delivery severe enough to result in HIE will show other signs of hypoxic damage including all the following:

1. Cord arterial blood pH <7

2. Apgar 0-3 at 5 minutes

3. Neurological sequelae and [multi organ dysfunction]

Human brain usually does not have the ability to store energy substrates. It needs constant supply of glucose and oxygen to meet its metabolic demands. Under normal circumstances each glucose molecule gets metabolized to produce 38 molecules of ATP. When there is tissue hypoxia energy supply is by anaerobic glycolysis which yields only 2 molecules of ATP per glucose broken down and also results in production of lactic acid. Lactate can cause a breakdown of the blood brain barrier and also contribute to cerebral oedema. It also along with increased carbondioxide leads to impaired vascular autoregulaton, inhibition of glycolysis and direct tissue injury. [19]

Cerebrovascular blood flow in HIE

When there is asphyxia injury, the body tries to maintain the blood flow to the brain by redistributing the cardiac output. This autoregulatory mechanism can result in an increase in cerebral blood flow upto 30-175 times. This increase in cerebral blood flow is achieved locally by a reduction in cerebrovascular resistance and systemically by hypertensive response. The cerebrovascular response largely depends on the severity and the speed of onset of the asphyxial insult [20]. But very severe asphyxia, if rapid in onset results in a decrease in

cerebral blood flow. This occurs probably due to increased cerebrovascular resistance. During periods of prolonged hypoxic-ischemic insult, these homeostatic mechanisms fail, and there is loss of cerebral vascular autoregulation , decrease in cardiac output , and systemic hypotension develops with reduced cerebral blood flow [20]

If the cerebral vasculature is normal the decrease in cerebral perfusion can be compensated for by rapid dilatation of smaller blood vessels in the brain. This mechanism helps to maintain a relatively constant cerebral blood flow as long as the systemic blood pressure is kept within the normal range. The term autoregulation is used for this constancy of cerebral blood flow in the face of fluctuations in systemic blood pressure.

In the neonatal brain the large cerebral blood vessels are believed to be more important for cerebral autoregulation than the arterioles, with the response to changes in blood pressure being endothelium dependent [21]. A number of chemical mediators have been implicated in the control of cerebral arterial tone [22]. The various mediators include Nitric oxide, which induces vascular dilatation by acting on the calcium-activated potassium channel of vascular endothelium. Adenosine also mediates vasodilatation, whereas endothelin-1 and prostanoids mediate vasoconstriction [21- 23] . Impairment of cerebral autoregulation can be caused by hypoxia, hypercarbia, and hypoglycemia. When autoregulation becomes defective as a result of a hypoxic injury, cerebral

arterioles fail to respond to changes in perfusion pressure and carbon dioxide concentrations, resulting in a pressure-passive cerebral blood flow. Pressure passive flow means that the cerebral blood flow now totally depends on the systemic blood pressure. An increase or decrease of the systemic blood pressure produces a similar increase or decrease in the cerebral blood flow.

When the process of ischemic insult ends there is a marked increase in cerebral blood flow, which is probably the result of various vasodilating factors already mentioned. This initial increase in cerebral perfusion is followed by a decline and a second, delayed increase in cerebral blood flow, probably the consequence of an increased synthesis of nitric oxide .Most of the deleterious events that lead to cell death within the brain occurs during this second phase.

Mechanisms of brain injury following hypoxic-ischemic event

Following a hypoxic-ischemic insult, neuronal death occurs in two major phases,

1) Primary neuronal cell loss which occurs at the time of the insult

2) Delayed neuronal cell loss which occurs later. [24]

During the time of the initial insult which is cellular hypoxia there is exhaustion of high-energy metabolism (primary energy failure) and cellular depolarization. When primary energy failure, studies suggest that there are three closely interrelated mechanisms which causes the neuronal cell death.

A) Firstly, hypoxia causes depolarization of the neuron leading to an influx of sodium and a lesser efflux of potassium with passive chloride entry along the electrochemical gradient. This results in cell swelling and, if sufficiently severe, cell lysis. (25)

B) Secondly, there is an intracellular accumulation of calcium ions. This is due to both excessive entry of calcium into the cell due to failure of ion channels and also failure to remove calcium by the sodium- calcium pump. (26)

C) Thirdly, there is extracellular glutamate accumulation (which acts as an excitatory neurotransmitter) due to failure of energy dependent re-uptake as well as excessive release. Elevated glutamate also acts as a key mechanism stimulating intracellular calcium accumulation through the N-methyl-D-aspartate (NMDA)-receptor-channel complex.

Further damage to cell membrane occurs due to the action of free radicals in the immediate reperfusion phase. (27) This secondary loss of neurons is termed secondary or delayed neuronal death. This phase is usually associated with hyperexcitability and cytotoxic edema from about 6 hours – 4 days after the injury, as found in a study on fetal sheep. (28)

Inflammatory mechanisms involved in hypoxia-ischemia

It has been found that there is an association between neonatal hypoxic-ischemic encephalopathy and inflammatory cytokines, the blood levels of

which is significantly elevated in term infants who later develop neurologic sequels especially cerebral palsy. [29] Elevated levels of IL-6 and IL-8 in the cerebrospinal fluid of term newborns is identified to be directly proportional to the degree of encephalopathy and poor neurodevelopmental outcome. [30] A study using MR Spectroscopy has demonstrated a correlation between elevated lactic acid level in the basal ganglia and serum IL-1, IL-6, IL-8 and TNFα levels in infants with HIE. [31] A few experimental animal studies in which newborn mice were subjected to unilateral carotid artery ligation show that there is an up-regulation of many inflammatory genes associated with cellular activation in the injured hemisphere of the brain.[32] The expression of inflammatory gene is evident at 8 h and increases further at 24 to 72 hours after the hypoxic ischemic insult, and the set of genes that is expressed suggests an activation of microglia and other inflammatory cells. [32] There is also increased expression of chemokines and infiltration of inflammatory cells around the lesion. [33] Microglial aggregation in the dentate gyrus has also been observed in human infants during the post hypoxia-ischemia period. [34] Microglia may contribute to secondary brain injury through the production and release of pro-inflammatory cytokines, proteases, reactive oxygen species, NO, complement factors, and excitotoxic neurotransmitters such as quinolinic acid.

Role of free radicals and reactive oxygen species in hypoxia-ischemia

When there are repeated episodes of hypoxia there is an accumulation of purine derivatives such as adenosine or hypoxanthine. This leads to specific changes that predispose cells to enhanced damage on reoxygenation. [35] There is activation of oxidases and nitrogen oxide synthase (NOS), and up-regulation of hypoxia inducible factor-1 alpha (HIF-1α), as well as downregulation of antioxidant enzymes, such as superoxide dismutases, catalases, and glutathione peroxidases. This generates a burst of reactive oxygen (ROS) species on reoxygenation. [36] There is also a marked increase in nNOS immunoreactivity in nerve fibers for more than a week after hypoxic ischemic insult in regions such as the thalamus. [37]

Apoptotic mechanisms involved in hypoxia-ischemia

Neonatal hypoxic-ischemic cell death has been shown to be associated with multiple apoptotic pathways. The post-mortem brain tissue of full term neonates with severe perinatal asphyxia has been found to contain elevated levels of activated caspases. [38] Hypoxia–ischemia causes an activation of Fas death receptor signaling in the neonatal brain. [39]

Classification

Classification of any disease process helps to assess the prognosis as well as to collect and compare research data which may be of later use. There have been

various school of thought for the classification of Hypoxic ischemic encephalopathy . The Sarnat and Sarnat grading of HIE was published in 1976 [40] in a study which related electroencephalographic findings to the clinical condition of the infants. This system of HIE grading is still widely used for the staging and prognosis of asphyxiated newborn. The Sarnat staging classifies HIE into three stages as is shown in the table below.

Hypoxic-Ischemic Encephalopathy in Term Infants

SIGNS	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalographic	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr to 14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

Amiel-Tison correlated MRI, EEG and VEP with Sarnat scoring system and Miller tried to compare it with information about feeding difficulties [41, 42] . Dubowitz developed a revised system based on Amiel-Tison scoring with an optimality score [43] applicable during the first days of life. The aim of Dubowitz's study was to evaluate the distribution of various findings and their possible variation with gestational age in the range of term birth (37-42wks) and to develop an optimality score to help identify abnormalities occurring in only a small minority of normal infants. Some of the variables used by Dubowitz included posture, arm recoil, arm traction, leg recoil, leg traction, popliteal angle, head control-flexor tone and extensor tone, head lag, and ventral suspension.

Another classification is by Levene, according to which HIE is typed as

a) *Mild (I)* showing Hyperalertness, normal /decreased spontaneous motor activity, mild hypotonia and poor suck
b) *Moderate (II)* showing seizures, lethargy, marked tone abnormality (arms > legs),and requirng tube feeding
c) *Severe (III)* characterised by coma, no spontaneous movements, severe hypotonia , prolonged seizures, and inability to maintain normal respiration

Newborns with mild encephalopathy have maximum symptoms during the first 24 hours and then it wanes off. These neonates exhibit jitteriness and increased

irritability. These babies do not have seizure activity and have a normal aEEG/EEG pattern and they always have a good prognosis. Neonates who deteriorate with altered levels of consciousness and clinical/subclinical seizure activity 12-24 hours after the hypoxic-ischemic event do so because would have developed moderate-severe HIE (II-III). Electrophysiology abnormalities are common in this group, including seizure activity and abnormal background pattern on aEEG. Grade III or severe HIE leads to loss of reflex activity, respiratory failure and coma. These most severe cases usually die or survive with major handicap. It is important to recognize the change in severity since there is a good correlation between HIE and outcome. The Thompson score [44] is a composite grading of encephalopathy signs. It looks at 9 characters in the baby which includes tone, loss of consciousness, seizures, posture, moros reflex, grasp, suck, respiration, and the fontanelle. Each of the character or variable is given a score from 0 to 3, where a score of 0 is considered as normal for each. At one year of age, it has a high predictive value: a peak score of 15 or higher has a positive predictive value of 92% and a negative predictive value of 82% for abnormal outcome, with a sensitivity and specificity of 71% and 96%, respectively. This score has been widely introduced as it correlates well to neurological outcome already during the first hours of life in contrast to the Sarnat score, which is reliable only after 24 hours. This is a reasonable system of scoring and is especially useful in areas where there are not many facilities for sophisticated investigations.

Role of electroencephalogram in hypoxic ischemic encephalopathy

The word electroencephalogram (EEG) denotes the graphs showing the signals obtained by identifying the potential differences between electrodes placed on the scalp. The definition for abnormal EEG may be different according to different schools of thought but paroxysmal activity lasting for more than 10 seconds is taken as seizure. EEG seizures in newborns may not be well sustained. Neonatal seizures usually have a focal onset, while generalized onset of spike and wave seizure discharge is very rare. Early EEG is now being well recognized as a reliable predictor of neurodevelopmental outcome in infants with hypoxic ischemic encephalopathy. [45] .In two of the randomized controlled trials [46, 47] of induced HT following perinatal asphyxia, aEEG was used as inclusion criteria for starting HT, for monitoring brain function and seizures during treatment. Electrical discharges which last for less than 10 seconds duration have been called as BIRDs (Brief Interictal Rhythmic Discharges or Brief Ictal Rhythmic Discharges). The exact significance of these brief discharges is not well understood. However it has been associated with seizures in the same or subsequent EEG and also with poor neuro-developmental outcome. [48]

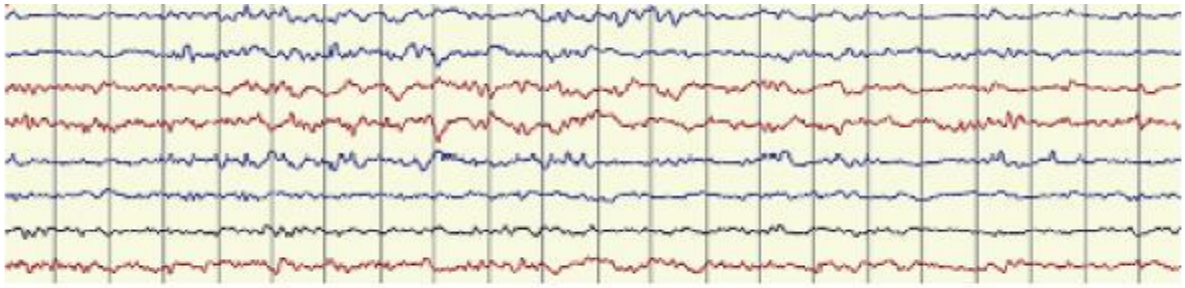
Though EEG can provide confirmation that any suspicious phenomena are seizures, not all clinically observed seizures are detected by EEG and many

neonatal seizures are subclinical (electro-cortical disassociation). There are 2 explanations for this phenomenon

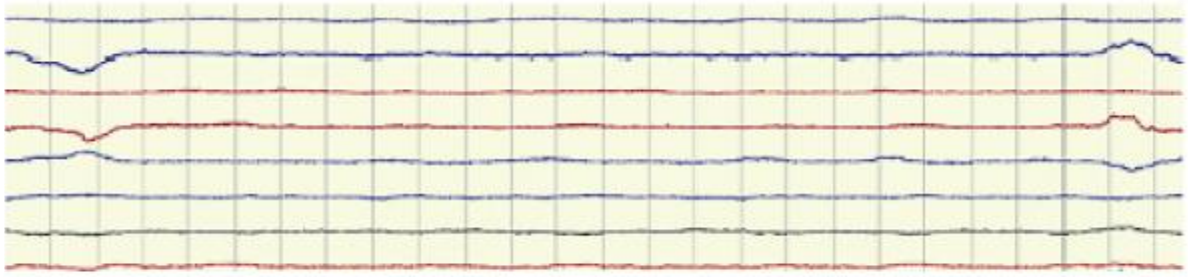
1) Some seizures may originate at a subcortical level and are not propagated to surface electrodes because of the immature synaptogenesis and cortical projections [(49)] and
2) Some subtle and tonic seizures might not be epileptic but are primitive brain stem and spinal motor phenomenae.

EEG patterns in newborns

1) Normal : continuous activity with physiological EEG patterns for behavioural states
2) Mildly abnormal : isolated temporal spikes, mild asynergy
3) Intermediate : predominant or transient discontinuous activity
4) Severely abnormal: inactive or permanent discontinuous activity (suppression burst or permanent discontinuous activity plus theta activity).[(16)]



normal



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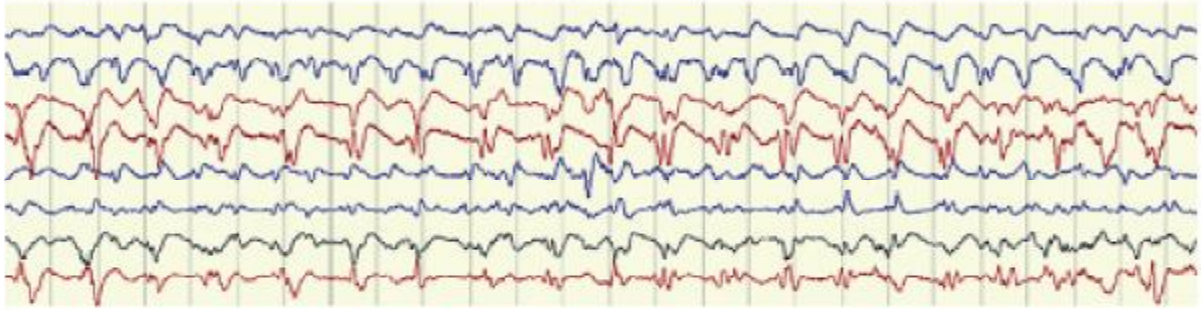
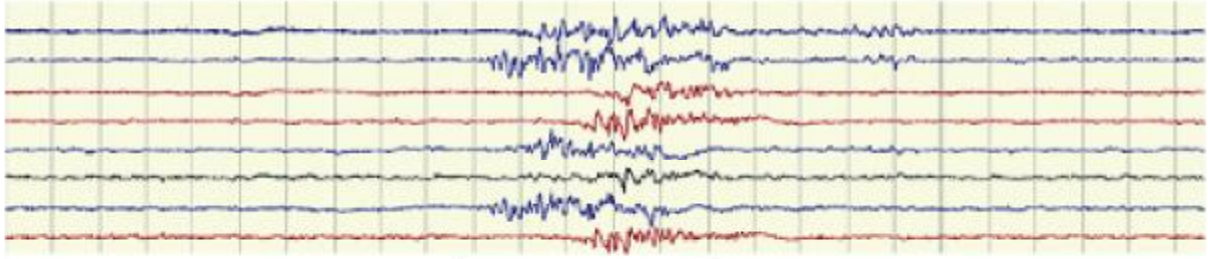


seizure



burst suppression

Imaging of the Neonatal Brain after Hypoxic-Ischemic Encephalopathy

Cranial ultrasound

This is a highly effective, non invasive portable technique used for urgent initial evaluation of the infant with hypoxic ischemic brain injury. The anterior fontanelle is the uaual window used for the procedure. But in about 50% of cases initial neurosonogram results may be negative. [51] However it is useful in the identification of injury to basal ganglia and thalamus especially hemorrhagic necrosis, focal and multifocal ischemic brain injury, and periventricular leukomalacia.

Computed tomography

CT scan though inferior to MRI can give important diagnostic information in identification of diffuse cortical injury in selective neuronal necrosis, injury to basal ganglia and thalamus, periventricular leukomalacia and focal and multifocal ischemic brain necrosis. But most of the findings in CT appear later – by the second week.

Magnetic resonance imaging (MRI)

Magnetic resonance (MR) imaging is the most accurate imaging modality in the diagnosis of hypoxic ischemic injury in newborn. The MRI findings of the brain

in neonates with hypoxic ischemic encephalopathy depend on the severity and duration of the insult and also the gestational age of the neonate [52, 53].

Major conventional MRI findings includes [19]

1) Cerebral cortical gray-white differentiation lost(on T1W or T2W)
2) Cerebral cortical high signal (T1W and FLAIR), especially in parasagittal perirolandic cortex.
3) Basal ganglia- thalamus, high signal(T1W and FLAIR, usually associated with the cerebral cortical changes but possibly alone with increased signal in brainstem tegmentum in cases of acute severe insult)
4) Parasagittal cerebral cortex, subcortical white matter, high signal(T1W and FLAIR)
5) Periventricular white matter, decreased signal(T1W) or increased signal(T2W)
6) Posterior limb of internal capsule, decreased signal (T1W or FLAIR)
7) Cerebrum in a vascular distribution, decreased signal (T1W) but much better visualized as decreased diffusion (increased signal) on diffusion weighted MRI

The T1- and T2-weighted images on MRI may appear normal during the first days after the hypoxic-ischemic event or it may show only subtle findings which may be difficult to interpret or to distinguish from normal (maturational) phenomena in the neonatal brain [52,54]. Temporal evolution in enhancement may

be seen on contrast material- enhanced imaging depending on the time of imaging after the hypoxic-ischemic insult as well as the duration and nature of the incident [55].

There are different scoring systems for the MRI data. These are the [56]

a) basal ganglia (BG) score – this particularly focuses on basal ganglia pattern of injury
b) Watershed score – this was to include the intervascular boundary zones in the gray and white matter perfused by the major cerebral arteries. Lower scores are given for less extensive damage and higher for more damage.
c) Basal ganglia/watershed(BG/W) score- this was made in an attempt to combine the basal ganglia and the watershed score.
d) Summation score(S) – this is also a combination of basal ganglia and the watershed score.

e) Enhancement score – based on the post contrast image.

Score	Finding
Basal ganglia score	
0	Normal or isolated focal cortical infarct
1	Abnormal signal in thalamus
2	Abnormal signal in thalamus and lentiform nucleus
3	Abnormal signal in thalamus, lentiform nucleus, and perirolandic cortex
4	More extensive involvement

Watershed score	
0	Normal
1	Single focal infarction
2	Abnormal signal in anterior or posterior watershed white matter
3	Abnormal signal in anterior or posterior watershed cortex and white matter
4	Abnormal signal in both anterior and posterior watershed zones
5	More extensive cortical involvement
Basalganglia/watershed score	
0	Normal
1	Abnormal signal in basal ganglia or thalamus
2	Abnormal signal in cortex
3	Abnormal signal in cortex and basal nuclei (basal ganglia or thalami)
4	Abnormal signal in entire cortex and basal nuclei
Summation (S) score	Arithmetic sum of BG and W score

Enhancement (E) score	
0	No enhancement
1	Enhancement in white matter only
2	Enhancement in deep gray matter nuclei
3	Enhancement in cerebral cortex
4	Enhancement in cortex and deep gray matter or white matter

Advanced MRI Applications

Magnetic Resonance Diffusion

Diffusion-weighted imaging (DWI) uses strong diffusion gradients that generate images based upon differences in the rate of diffusion of water molecules. Diffusion tensor imaging characterizes the rate and direction of white matter diffusion by providing visualization of fiber tract direction and integrity. This technique has been used to assess white matter fiber tracts in the immature brain, congenital disorders, acquired disorders of white matter, malformations of cortical development, effects of chemotherapy and radiation in patients with brain tumors, leukodystrophies, and hypoxic ischemic encephalopathy.

Cowan [(57)] found that 80% of studied infants with HIE had signs of acute injury on early DWI which was not established on later scans. There are two main

pattern of evolution of injury during the first 4-10 days: a) basal-ganglia-thalamus (BGT) pattern [58] and b) watershed injury pattern [59] . These patterns of injury are associated with the respective underlying causes:

i) acute HI event or

ii) prolonged partial HI event.

A BGT pattern with an abnormal signal in the posterior limb of internal capsule (PLIC) on T1W and T2W images is a robust marker for permanent injury and later sequelae. It has a high predictive value for adverse outcome [60] . Studies done using serial MRI scans have shown a evolution of the brain injury with acute changes during the first week of life, a pseudo-normalization during the second to third week and later newly affected areas of the brain showing permanent loss of tissue correlating to functional outcome [56] . Diffusion-weighted imaging helps in early detection of cytotoxic edema.

MR Spectroscopy (MRS)

Studies with MR Spectroscopy (MRS) have defined a subgroup of infants with characteristic hypoxic-ischemic injury and have permitted non-invasive observation of brain metabolism after the insult [61,62] . MRS is considered as the most sensitive modality for the detection of neonatal brain disturbance in the acute period. [19] Studies have shown a characteristic pattern of energy failure in infants with moderate-severe HIE who were scanned repeatedly with MRS and

followed for 1-4 years. Immediately after the hypoxic ischemic injury, the intracerebral energy storage is normal. This is followed by a decline within 6-15 hours, showing ATP depletion and an increase in lactate [63] . MRS is especially useful when the cytotoxic edema is still evolving, during the first day of life, and before any structural changes have been established. The presence of lactate is always pathological and it can remain elevated for several months after the insult.

Near-infrared spectroscopy

Cerebral near-infrared spectroscopy(NIRS) monitoring uses light in the near-infrared region of the spectrum, which is absorbed by oxygenated and deoxygenated hemoglobin (total hemoglobin is taken as an index of cerebral blood volume) and cytochrome oxidase (CytOx), which is the terminal complex of the mitochondrial respiratory chain and generator of ATP. [64, 65] Using NIRS it has been demonstrated that during recovery from severe asphyxia there is a brisk restoration of blood volume, oxygenation and oxidative metabolism. [66] During the early recovery phase after asphyxia, CytOx activity returns to normal. This transient stable phase is followed by progressive loss of CytOx activity, accompanied by a relative reduction in brain oxygenation extraction consistent with mitochondrial failure

Positron Emission Tomography (PET)

Positron emission tomography (PET) uses radio-labelled isotopes to measure in vivo biochemical and physiological changes in the brain during health and disease. Using 18 FDG-PET, an acute increase in glucose utilization has been shown in areas corresponding to the later diagnosed neurological deficits [67, 68] . This finding might reflect presence of viable neurons and the possibility of on-going pathological processes in them. Repeating the scan at 2-4 weeks after the insult, shows decreased glucose utilization in the same area, probably reflecting permanent cell damage. PET remains a highly elaborate examination only available at a few research centers in the world, but has contributed important insights into the pathology of evolving brain damage.

Aims and objectives of the study

In a term newborn with hypoxic ischemic encephalopathy

1) To correlate the electroencephalogram and computed tomography of brain done in the newborn period with the neurological outcome
2) To correlate the magnetic resonance imaging of brain done at 3 months of age with the neurological outcome
3) To compare the usefulness of electroencephalogram, computed tomography and magnetic resonance imaging of brain in predicting the neurological outcome at one year.

Materials and methods

Study Design	:	Prospective Study
Study place	:	PSG Institute of Medical Sciences and Research, Coimbatore .
Study period	:	From June 2009 to November 2011
Study population	:	Term newborns (inborn and outborn) admitted in the Newborn Intensive Care Unit of PSG hospital with history of birth asphyxia.
Sample size	:	31 term newborns
Study approval	:	Ethics committee PSG IMS & R

Inclusion criteria :

1) Term neonates ≥ 37 weeks gestational age

2) Perinatal asphyxia defined as presence of two or more of the following[16]
   a) Signs of fetal distress as indicated by one or more of the following:
      - Fetal bradycardia (≤ 100 beats/min)
      - Thick meconium staining of liquor
      - Abnormal cardiotocography recordings.
      - Arterial cord pH < 7.2 or base deficit > 15mmol/L
   b) Apgar score < 6 at five minutes of life.
   c) Need for > 1 minute of positive pressure ventilation before occurrence of sustained respiration

Exclusion criteria :

1) Preterm neonate
2) Major congenital anomalies
3) Inborn error of metabolism
4) Low Apgar score due to maternal sedation

Method of data collection:

All term asphyxiated newborns admitted to the NICU between June 2009 and November 2010 who fulfilled the inclusion criteria were included in the study.

Informed written consent was obtained from the parents. Relevant data of both the mother and the baby were collected (Proforma enclosed) . Details of the mother included pregnancy status, number of live issues, complete antenatal history, mode of delivery and indication if it was instrumental or LSCS. Details of the baby included the presence of fetal distress, Apgar score (at 1 min and 5 min), need for resuscitation as well as its details. In the case of outborn babies, thse details were collected personally from the referring pediatrician and obstetrician.

The neonates were classified according to Sarnat and Sarnat staging for hypoxic ischemic encephalopathy. The presence of seizures was recorded as were the anti -convulsant drugs used in each case.

All cases had an EEG recorded as soon as the baby was stable, most within the first 72 hrs, latest by day 5 of life .EEG recording was done using RMS (recorders and medicare system) recorder and the electrodes were placed according to 10-10 system which is the internationally recommended system for infants. The EEG recordings were reported by a single trained neurologist. The different patterns in EEG were classified into

1) Normal continuous activity
2) Isolated temporal spikes
3) Transient discontinuous activity
4) Suppression burst / Permanent discontinuous activity

A computed tomography of the brain was done for the babies using Seimens somatom sensation 64 slice machine. The CT scan was done between 72 hrs of life and the 7th day. CT was preferred over MRI at this stage due to the need for deep sedation for the latter which increased ther risk of respiratory depression in the already asphyxiated baby. The CT scan was reported by a trained radiologist and the findings were documented as normal/ cerebral oedema and other changes such as intracranial or extracranial bleeds, and areas of hypodensities.

A Magnetic Resonance Imaging was done at 3months of age by using Seimens Avantom 1.5 Tesla machine using multichannel headcoils under sedation. The MR sequences that were employed were T2, T1, FLAIR, Diffusion, susceptibility weighted and inversion recording imaging. The MRI was reported by a different trained radiologist who was unaware of the CT scan findings or clinical status of the baby. The findings were classified according to basal ganglia/ watershed pattern as described by Barkovich [(56)]. Normal score 0, abnormal signal in basal ganglia or thalamus score 1, abnormal signal in cortex score 2, abnormal signal in cortex and basal nuclei (basal ganglia or thalami) score 3, abnormal signal in entire cortex and basal nuclei.

All babies were followed up regularly at 3, 6 and 12 months of age. During the follow up period, seizure recurrences and need for anticonvulsant medications were noted and recorded. At 12 months of age they were all subjected to a complete neurodevelopment assessment by the author in association with one of the senior consultants in the department. Developmental screening was done using Denver Developmental Screening Test II (DDST II). While doing DDST II the items intersected by and just adjacent to the age line were tested. The items were denoted as P for pass, F for failed, No for no opportunity, and R for refused to cooperate or attempt. The interpretation of the individual items were made as follows

a) Advanced : Child passes item that falls completely to the right of the age line
b) Normal : Child passes, fails, or refuses item on which the age line falls between the 25^{th} and 75^{th} percentile
c) Caution : Child fails or refuses item on which the age line falls between the 75^{th} and 90^{th} percentile.
d) Delayed : Child fails or refuses item that falls complexly to the left of the age line
e) No opportunity : Child has had no chance to perform the item(taken only for report items)

DDST II test interpretation was done as

i) Normal : child with no delays and a maximum of 1 caution

ii) Suspect : two or more cautions and or one or more delays

iii) Untestable: refusal scores on 1 or more items completely to the left of age line or; more than one item intersected by the age line in the 75-90th percentile area. These children were rescreened again

Infants with a normal neurological examination and passed DDST II were considered as normal neurodevelopmental outcome and those who had an abnormal neurological examination and or failed DDST II were taken as poor neurodevelopmental outcome.

Statistical Methods:

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions:

1. Dependent variables should be normally distributed,

2. Samples drawn from the population should be random, Cases of the samples should be independent

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Diagnostic statistics viz. Sensitivity, Specificity, positive predictive value (PPV), negative predictive value(NPV) and Accuracy have been computed to find the correlation of ECG,CTandMRI brain with abnormal outcome

. **1. Sample Size estimation**

Proportion Known populations

$$n = [(z^2 * p * q) + ME^2] / [ME^2 + z^2 * p * q / N]$$

Proportion Unknown population

$$n = [(z^2 * p * q) + ME^2] / (ME^2)$$

ME: is the margin of error, measure of precision.

and Z is 1.96 as critical value at 95%CI

N: population size

n: Sample size

σ: Standard deviation

z: Critical value based on Normal distribution at 95% Confidence Interval

Standard deviation: $SD = \sqrt{\frac{\sum (x - \bar{x})^2}{n-1}}$

The following statistics can be defined:

- *Sensitivity*: probability that a test result will be positive when the disease is present (true positive rate, expressed as a percentage).

  = a / (a+b)

- *Specificity*: probability that a test result will be negative when the disease is not present (true negative rate, expressed as a percentage).

  = d / (c+d)

- *Positive predictive value*: probability that the disease is present when the test is positive (expressed as a percentage).

  = a / (a+c)

- *Negative predictive value*: probability that the disease is not present when the test is negative (expressed as a percentage).

  = d / (b+d)

- *Accuracy is the sum of true positive and True negative divided by number of cases*

2. Diagnostic values based on accuracy

0.9-1.0 Excellent test

0.8-0.9 Good test

0.7-0.8 Fair test

0.6-0.7 Poor test

0.5-0.6 Fail

3. Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results

There were a total of forty two newborns with birth asphyxia admitted in the newborn ICU during the study period. Two of the term asphyxiated babies had an inborn error of metabolism so were not included in the study. Two infants were excluded due to major congenital anomaly namely complex cyanotic heart disease and a severe central diaphragmatic hernia. Seven infants were preterm and did not satisfy the inclusion criteria. The remaining thirty one term newborns who satisfied the inclusion criteria were included in the study.

The selected thirty one which included twenty four males and seven females were assessed according to the study plan by doing an EEG, CT and MRI brain and followed up till 1 year of age. Of the 31, four infants died within the first three months of life and one was lost to follow up.

Table 1: Birth weight of babies studied

Birth weight (kg)	Number of babies	%
2.0-2.5	1	3.2
2.5-3.0	18	58.1
3.0-3.5	9	29.0
>3.50	3	9.7
Total	31	100.0

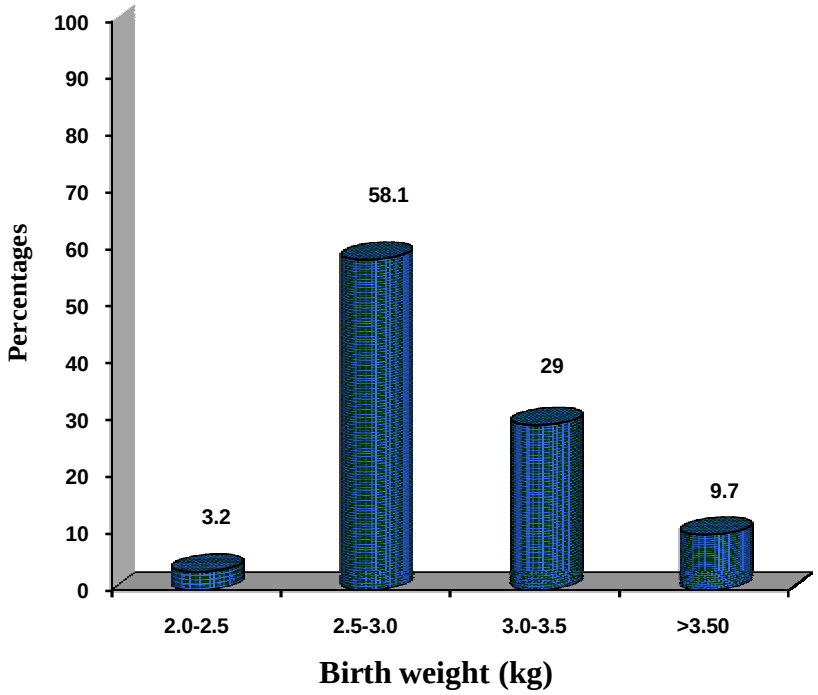


Table 2: Gender distribution

Gender	**Number of babies**	**%**
Male	24	77.4
Female	7	22.6
Total	31	100.0

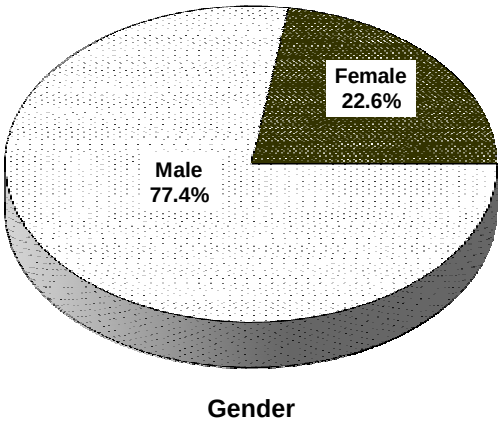


Table 3: In born /Outborn

Inborn/Outborn	Number of babies	%
Inborn	10	32.3
Outborn	21	67.7
Total	31	100.0

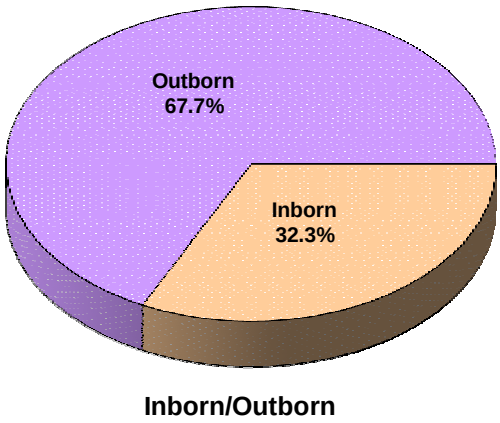


Table 4: Order of birth

Order of birth	Number of babies	%
1st	26	83.9
2nd	5	16.1
3rd	0	0.0
4th	0	0.0
Total	31	100.0

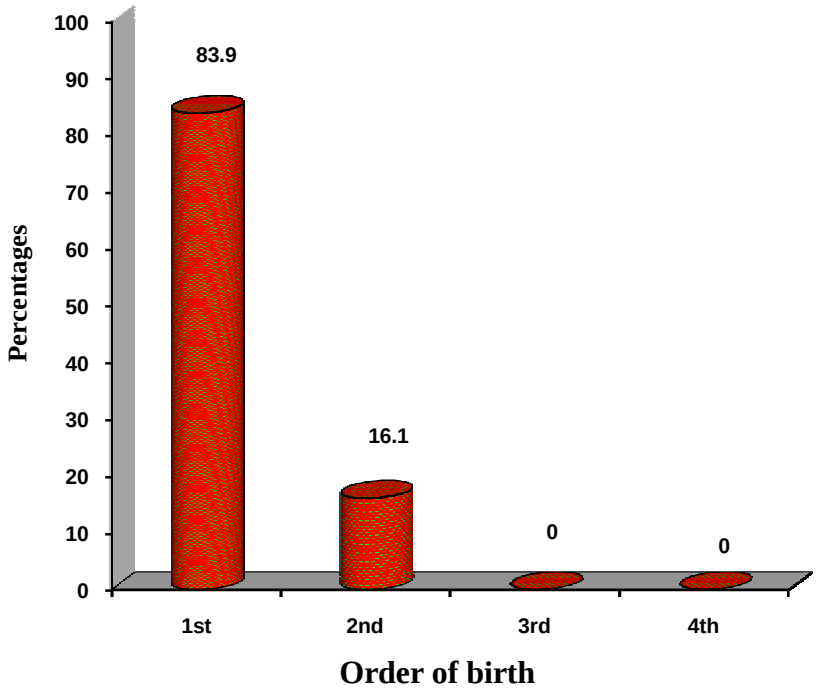


Table 5: Mode of delivery

Mode of delivery	Number of babies	%
Normal	7	22.6
Instrumental	11	35.5
LSCS	13	41.9
Total	31	100.0

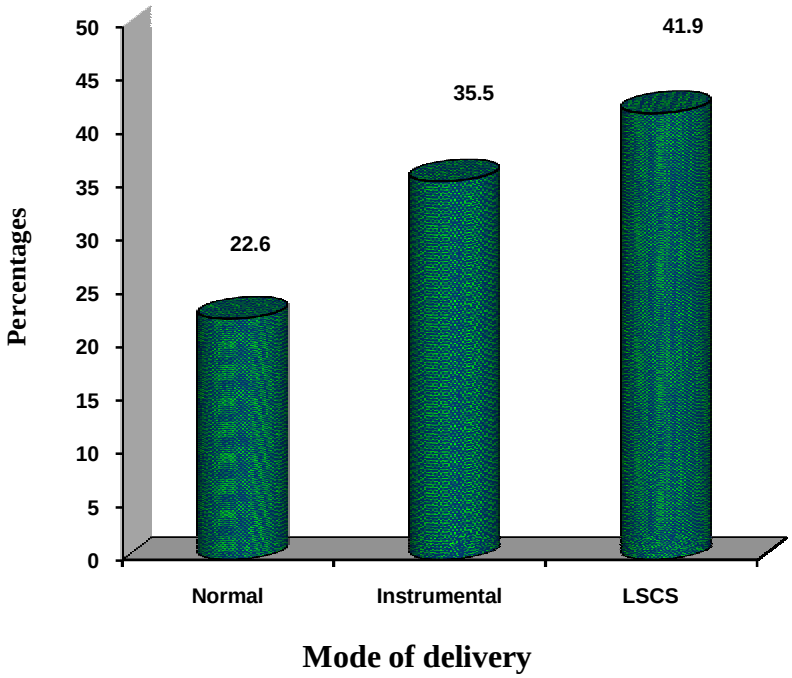


Table 6 Indication of LSCS

Indication	**Number of babies (n=24)**	**%**
Fetal	13	54.2
Maternal	2	8.3
Both	9	37.5

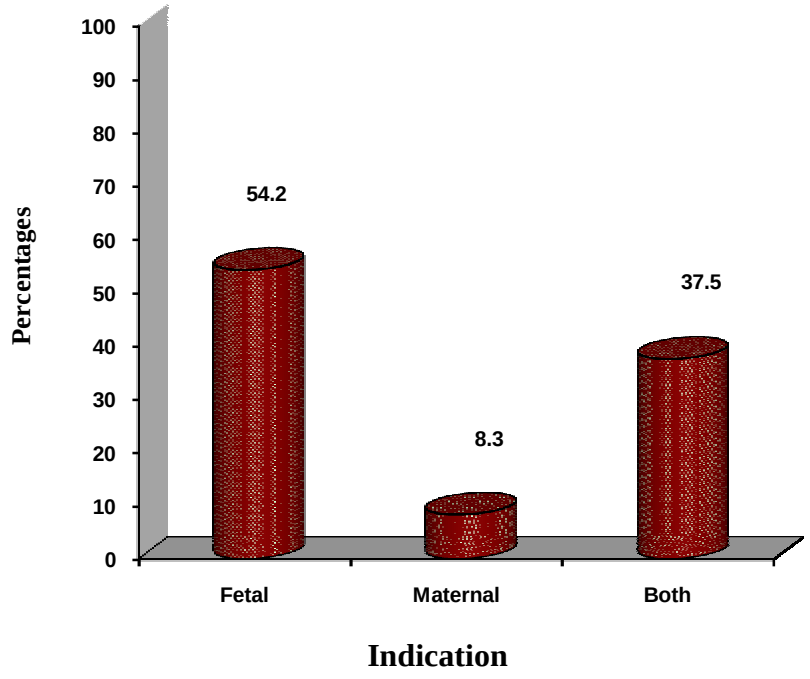


Table 7: Sarnat stage

sarnat stage	Number of babies (n=31)	%
I	9	29.0
II	13	41.9
III	9	29.0

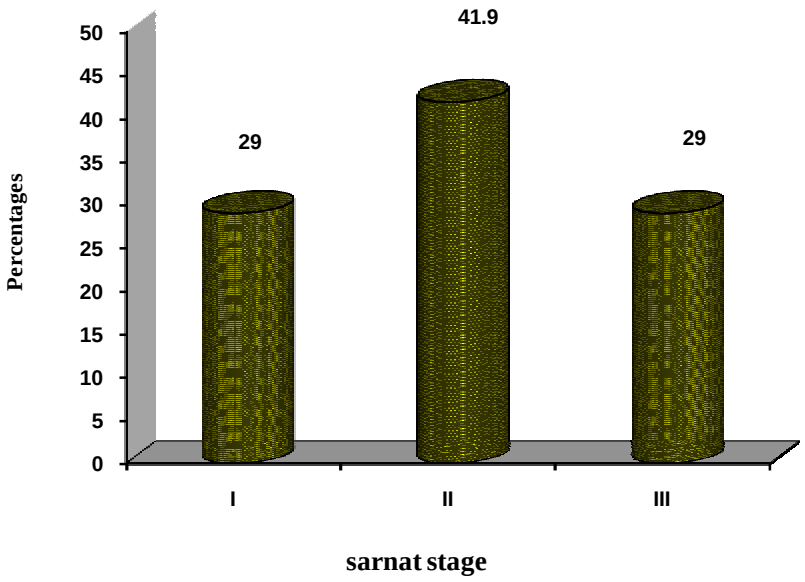


Table 8: Type of Seizures

Type of Seizures	**Number of babies (n=31)**	**%**
Subtle	3	9.7
Focal	7	22.6
Generalized	12	38.7
Myoclonic	9	29.0

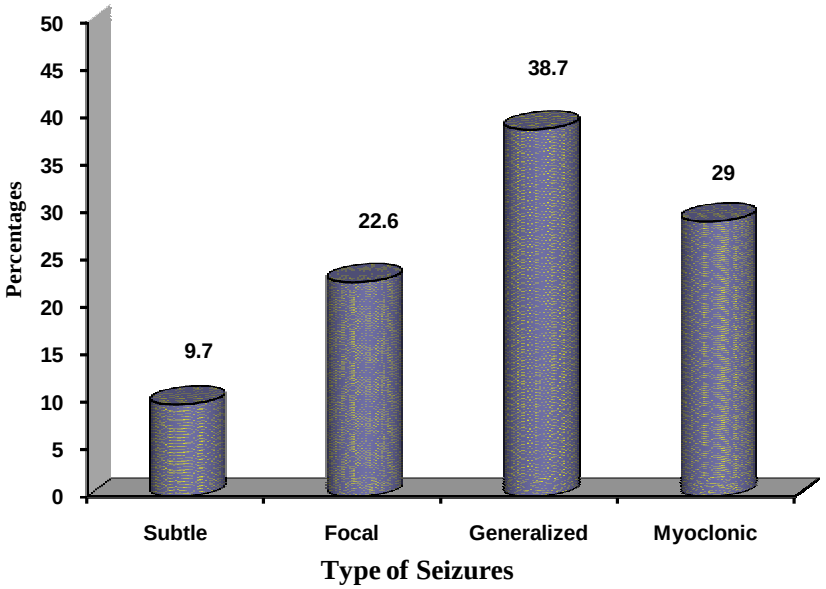


Table 9: Antiepileptic drug

Antiepileptic drug	**Number of babies (n=31)**	**%**
Single drug	8	25.8
2 or more	21	74.2

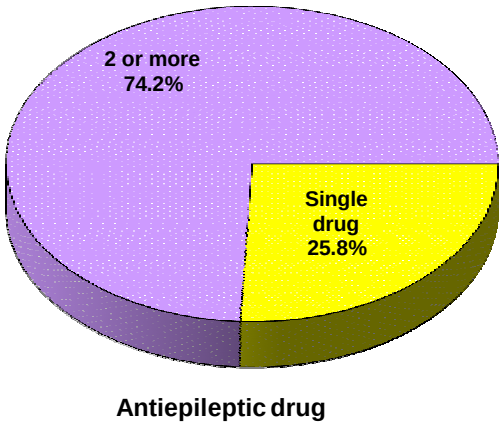


Table 10: Seizure control

Seizure control	**Number of babies (n=31)**	**%**
<24 hrs	8	25.8
24-72 hrs	9	29.0
4-7 days	11	35.6
>7 days /uncontrolled	3	9.7

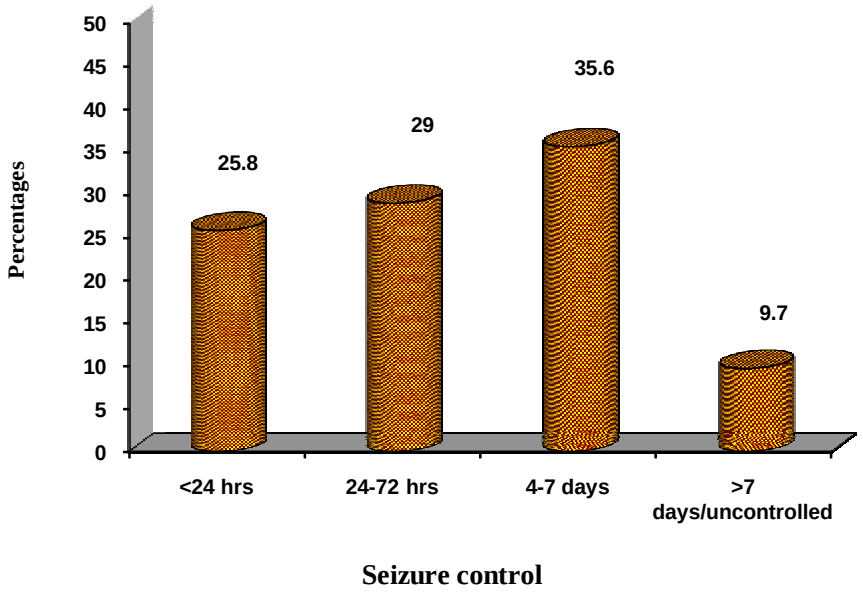


Table 11: The number of anti-epileptic drug at time of discharge.

Discharge anti-epileptic	**Number of babies (n=31)**	**%**
Nil	0	0.0
Single	30	96.8
>1	1	3.2

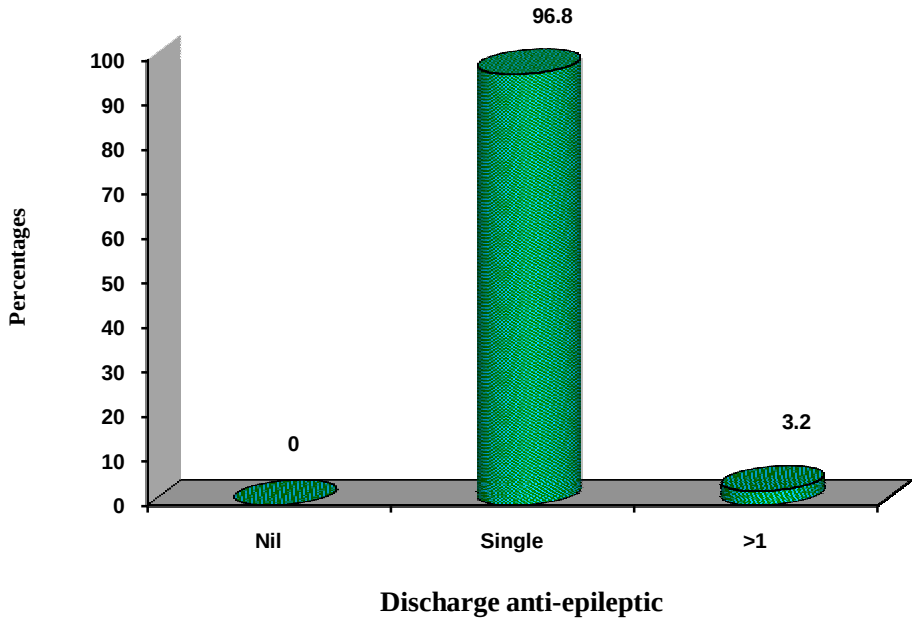


Table 12: EEG pattern

EEG pattern	**Number of babies (n=31)**	**%**
Normal continuous activity	6	19.4
Isolated temporal spikes	4	12.9
Transient discontinuous activity	7	22.6
Permanent discontinuous activity/Suppression burst	14	45.2

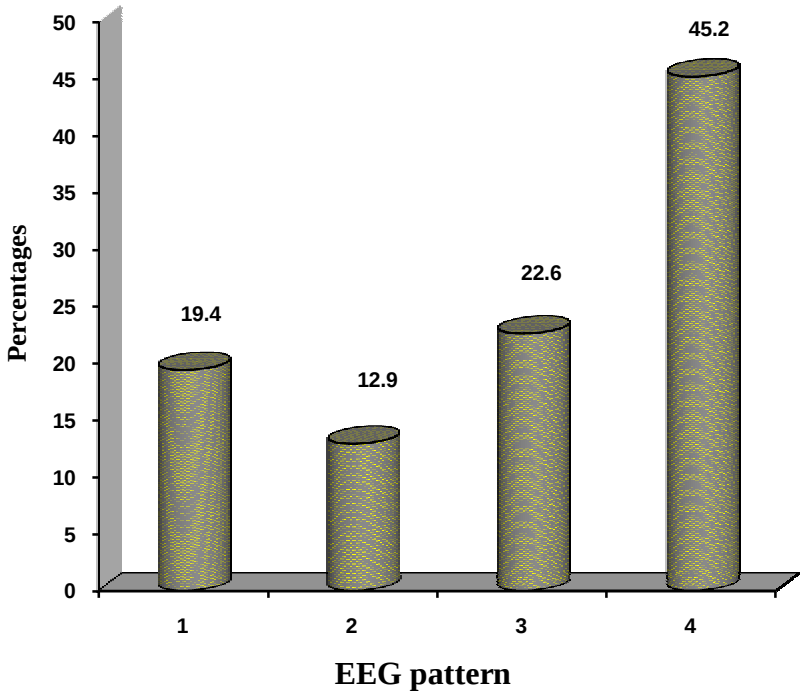


Table 13: CT brain findings

CT findings	**Number of babies (n=31)**	**%**
Nil	14	45.2
Oedema	12	38.7
Others*	5	16.1

Other*- changes like Left frontoparietal and temp lobe wedge shaped hypodensity ,White matter hypodensity, sub arachanoid hemorrhage , sub galeal bleed, loss of gray and white matter differentiation

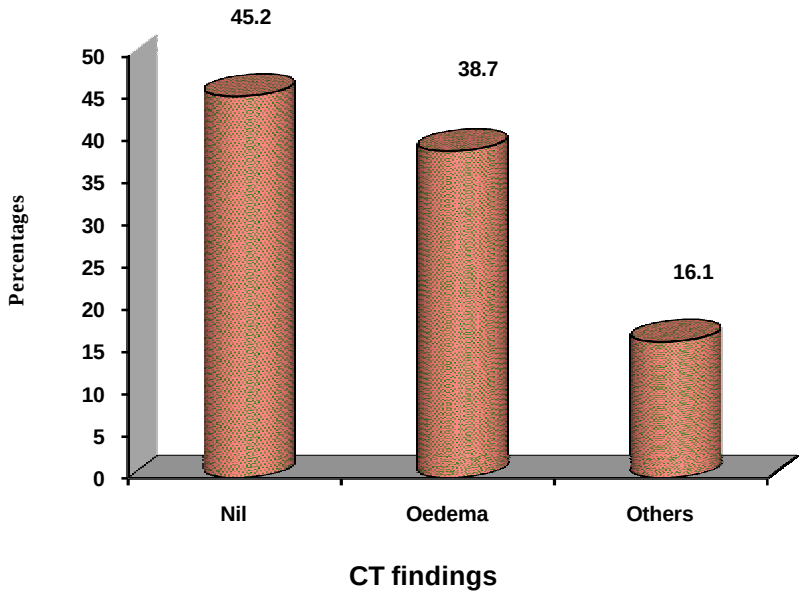


Table 14: MRI brain findings

MRI findings	Number of babies (n=26)	%
Normal	16	61.5
Abnormal signal in basal ganglia or thalamus	2	7.7
Abnormal signal in cortex	2	7.7
Abnormal signal in cortex and basal nuclei (basal ganglia or thalami)	6	23.1
Abnormal signal in entire cortex and basal nuclei	0	0.0

4 cases are Not available due to death before the investigation, 1 No Follow up

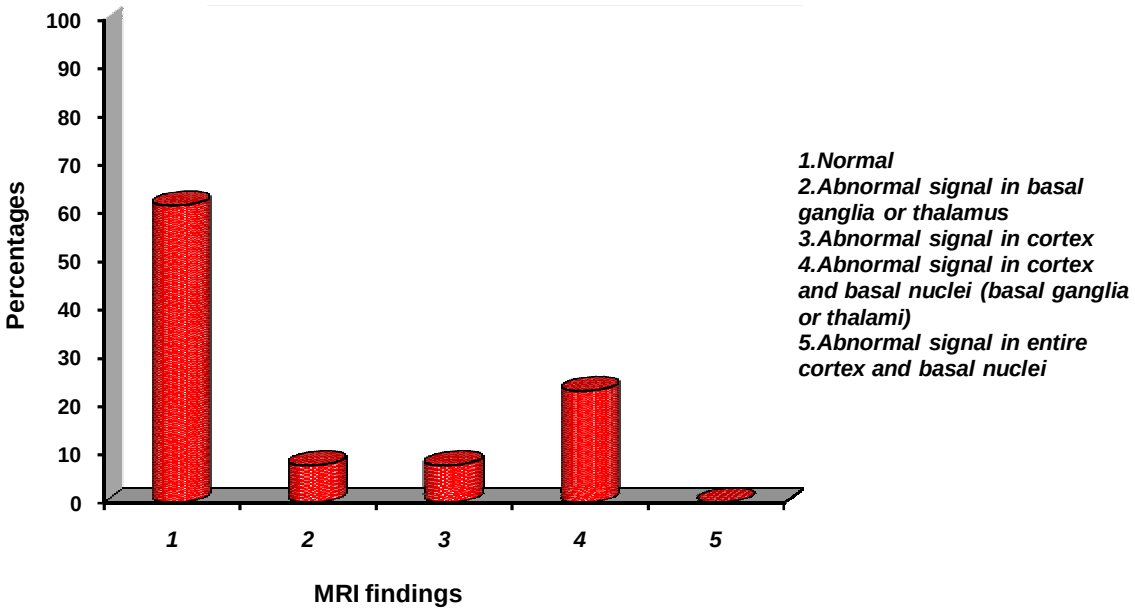


Table 15: Seizure recurrence

Seizure recurrence	**Number of babies (n=28)**	**%**
No	23	82.1
Yes	5	17.9

2 cases died hence not available, No follow up-1

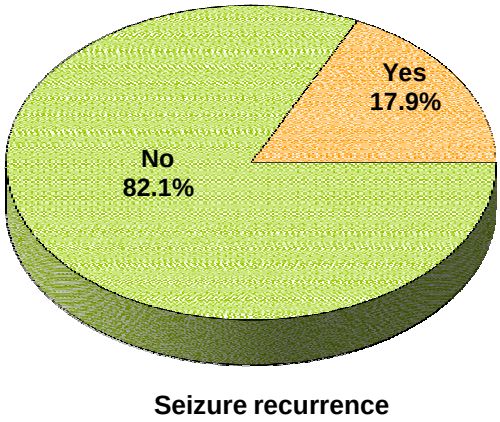
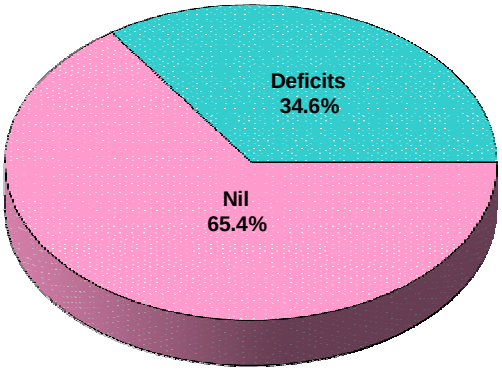


Table 16: Neuro-assessment at 12 months

Neuro assessment at 12 months	**Number of babies (n=26)**	**%**
Nil	17	65.4
Deficits	9	34.6

4 cases assessment not done due to death hence not available(NA), No follow up-1



Neuro assessment at 12 months

Table 17: DDST2

DDST2	**Number of babies (n=26)**	**%**
Normal	15	57.7
Suspect	11	42.3
Untestable	0	0

4 cases assessment not done due to death hence not available (NA), No follow up-1

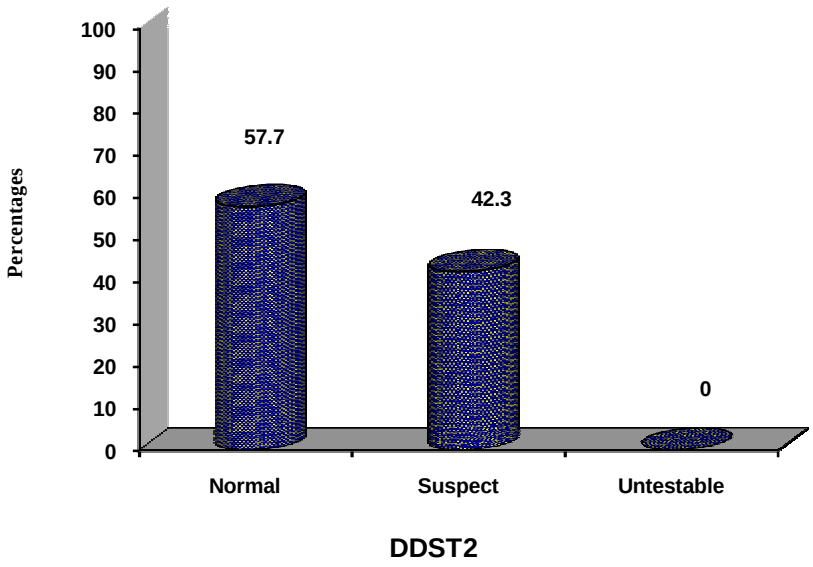


Table 18: Outcome

Outcome	Number of babies (n=30)	%
Normal	15	50.0
Abnormal	15	50.0

The abnormal outcome also includes cases which died. One case No follow up

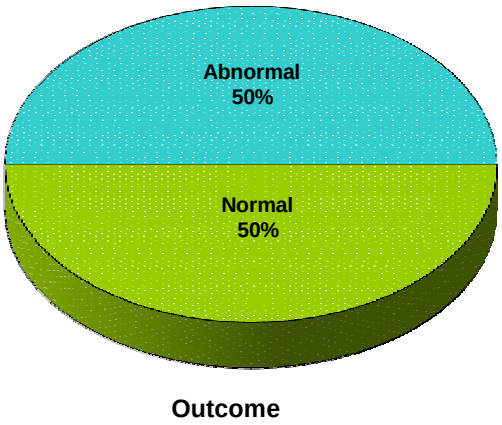


Table 19: Correlation of EEG with the outcome

EEG pattern	Normal outcome		Abnormal Outcome#		P value
	No	%	No	%	
Normal continuous activity	6	40.0	0	0.0	0.017*
Isolated temporal spikes	4	26.7	0	0.0	0.100
Transient discontinuous activity	5	33.3	2	13.3	0.390
Permanent discontinuous activity/Suppression burst	0	0.0	13	86.7	<0.001**
Total	15	100.0	15	100.0	-

death 4 & Abnormal-11

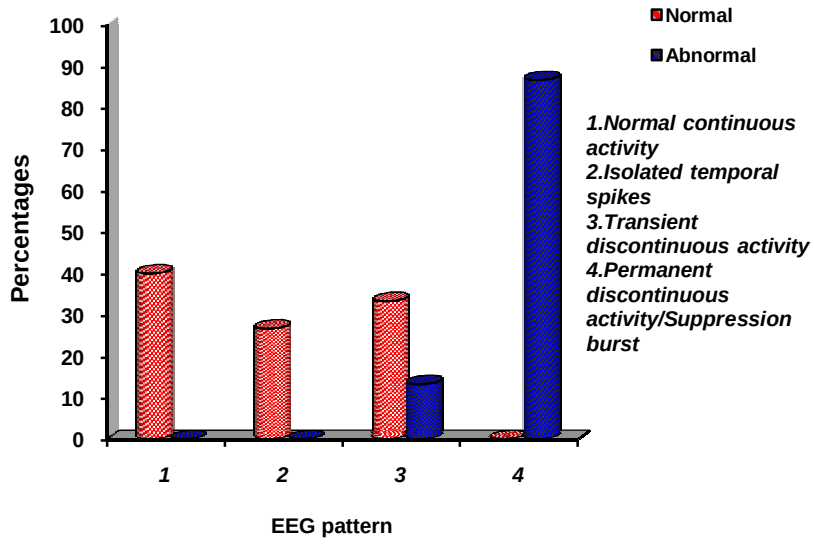


Table 20: Correlation of CT with the outcome

CT	Normal outcome		Abnormal Outcome#		P value
	No	%	No	%	
Nil	14	93.3	0	0.0	<0.001**
Oedema	1	6.7	11	73.3	<0.001**
Others	0	0.0	4	26.7	0.100
Total	15	100.0	15	100.0	-

death 4 & Abnormal-11

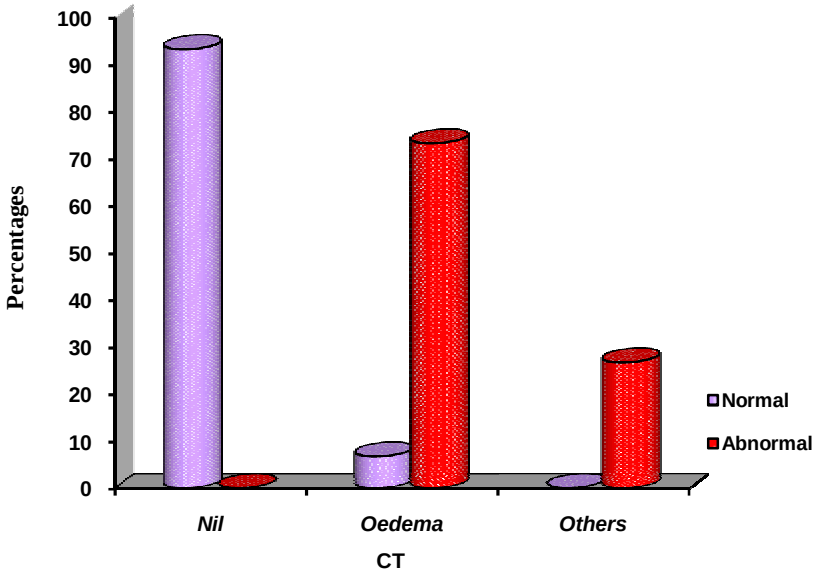


Table 21:Correlation of MRI with the outcome

MRI	Normal outcome		Abnormal Outcome#		P value
	No	%	No	%	
Normal	14	93.3	2	18.2	<0.001**
Abnormal signal in basal ganglia or thalamus	0	0.0	2	18.2	0.169
Abnormal signal in cortex	1	6.7	1	9.1	1.000
Abnormal signal in cortex and basal nuclei (basal ganglia or thalami)	0	0.0	6	54.5	0.002**
Abnormal signal in entire cortex and basal nuclei	0	0.0	0	0.0	-
Total	15	100.0	11	100.0	-

Abnormal-11

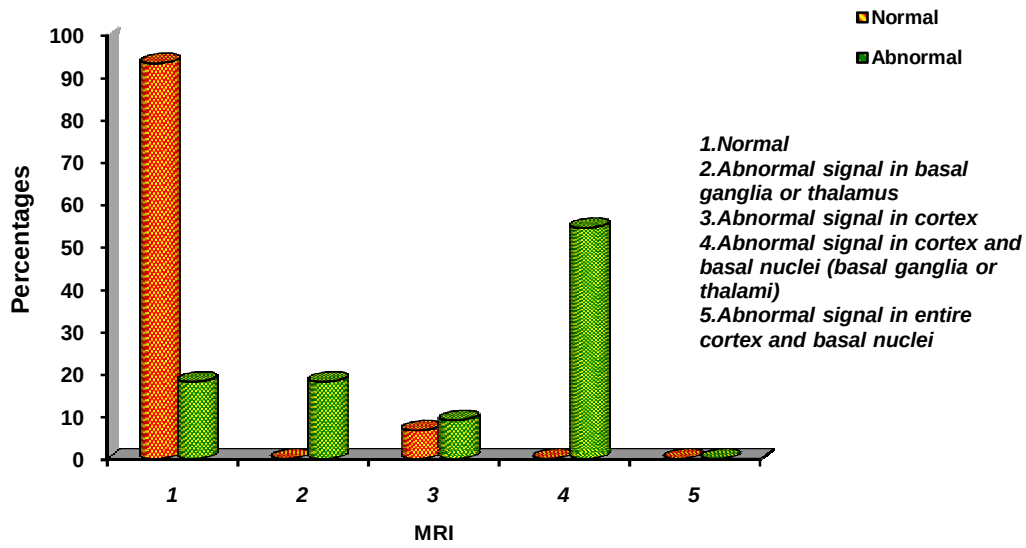


Table 22: Predictive ability of EEG, CT and MRI for predicting the abnormal outcome

	Sensitivity	Specificity	PPV	NPV	Accuracy	P value
EEG pattern	100.00	40.00	59.09	100.00	67.86	0.010*
CT	100.00	93.33	93.75	100.00	96.67	<0.001**
MRI(26 cases)#	81.82	93.33	90.00	87.50	88.46	<0.001**
MRI[@]	86.67	93.33	92.86	87.50	90.00	<0.001**

death 4 & Abnormal-11

@ four deaths included as abnormal MRI

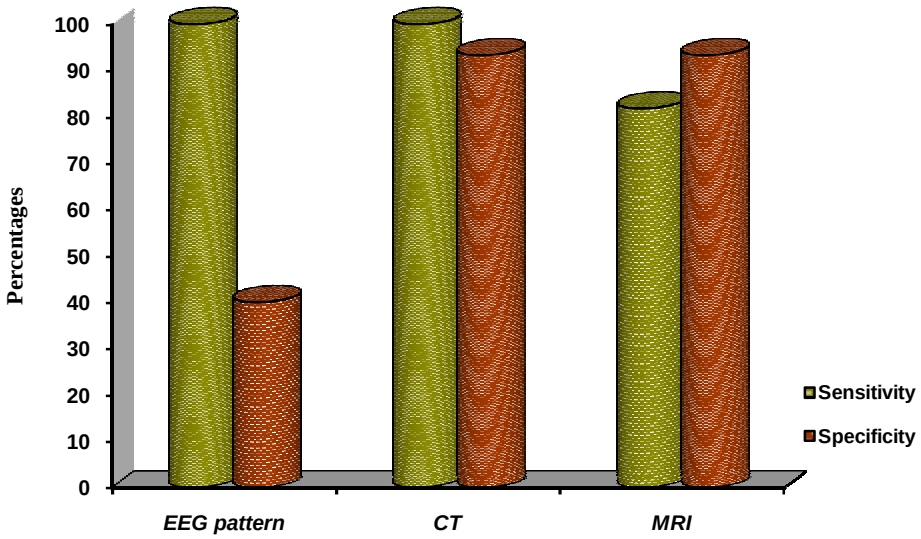


Table 23: Predictive ability of combined EEG+CT, EEG+MRI for predicting the abnormal outcome

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**	**P value**
EEG+CT	100.00	33.33	60.00	100.00	66.62	0.042*
EEG+MRI	100.00	40.00	55.00	100.00	65.38	0.024*
EEG+MRI@	100.00	40.00	62.50	100.00	70.00	0.017*

@ 4 death cases considered as abnormal

DISCUSSION

This study was done to correlate the neurological outcome of term newborns having hypoxic ischemic encephalopathy with findings of EEG and CT scan (done in the newborn period) and MRI Scan (done by three months). The secondary aim was to compare their relative usefulness in predicting neurodevelopment in these infants at one year of age.

EEG and its correlation

Of the 31 cases, EEG was normal in 6(19.4%), while 4(12.9%) had isolated temporal spikes, 7(22.6%) had transient discontinuous activity and 14(45.2%) babies had suppression burst pattern. All babies who had shown suppression burst pattern either had Sarnat stage 2 or stage 3 hypoxic ischemic encephalopathy.

All the 6 newborns with normal EEG were neurologically and developmentally normal at one year (p 0.017). 13 of the 14 babies with suppression burst pattern (one case lost to follow up) had an adverse outcome - death, neurological deficit or were suspect in the DDST 2 assessment (p <0.001) .

In our study, EEG in the newborn period has a sensitivity of 100% and specificity of 40% in predicting neurological outcome at one year. It has a positive predictive value of 59.09%, a negative predictive value of 100% and accuracy of 67.86(Table 22)

Ong L C et al have reported that EEG in asphyhxiated newborns has a PPV of 100%, NPV of 80.6%, sensitivity of 53% and specificity of 100% [16]. In a study on 77 asphyxiated infants by Caravale et al, among those with a normal early EEG (within 7 days of life) 83% were normal at one year of age while the remaining17% had only mild neurodevelopment abnormality [69] .

The negative predictive value of a normal EEG is emphasized by D M Murray et at [45] who concluded that a normal or mildly abnormal EEG within 6 hours of life is associated with normal neurodevelopment at 24 months. Our study has shown a 100% NPP for a normal EEG.

A suppression burst pattern on EEG in the newborn period is associated with a very high likelihood of an unfavorable outcome [70,71,72,73,74,75,76]. In a study by Grigg et al, out of 15 term infants with burst suppression on EEG, 14 had poor outcome [72]. Results of our study are in agreement with this observation.

CT brain and its correlation

Of the 31 babies, CT brain was normal in 14 (45.2%) ,while 12(38.7%) had cerebral edema of varying degree and 5(16.1%) had other findings like left frontoparietal and temporal lobe wedge shaped hypodensity ,White matter hypodensity, Sub arachanoid hemorrhage, sub-galeal bleed and thalamic hypodensity with loss of gray and white matter differentiation.

All those with normal CT scan had normal neurodevelopment outcome ($p < 0.001$). While 11 of the 12 with only cerebral edema had abnormal outcome ($p <0.001$) , 4 out of the 5 with specific findings in CT also had an abnormal outcome (p -0.1, not significant). Our study showed that an early CT brain has a sensitivity of 100%, specificity of 93.3%, PPV of 93.75%, NPV of 100% and accuracy of 96.67 in predicting neurodevelopment outcome at 1 year ($p < 0.001$)(Table 22). Our results are consistent with the observations of Volpe J J that infants with normal CT scans rarely exhibit major neurological deficits on follow-up and infants with scans demonstrating marked diffuse hypodensity rarely are normal on follow-up [(19)] .

MRI and its correlation

Of the 31 cases in the study, only 26 had an MRI brain(4 deaths and 1 lost to follow up). Among them, 16(61.5%) had normal MRI, 2(7.7%) showed abnormal signals in the basal ganglia/ thalamus, 2(7.7%) showed abnormal signals in the cortex and 6(23.1%) showed abnormal signals both in the cortex and basal ganglia

Out of the 16 with normal MRI, 14 infants had normal neurodevelopment at one year. The two remaining cases had normal neurological assessment, but were classified as suspect in DDST. All the 6 which had abnormal signals both in the cortex as well as thalamus had abnormal outcome (p 0.002). In the final analysis MRI brain has a sensitivity of 81.82%, specificity of 93.3%, PPV of 90%, NPV of 87.5%, accuracy of 88.46 in predicting the outcome at 1 yr of age ($p < 0.001$) Table 22). If it is assumed that the MRI of the 4 infants who died were also abnormal, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy are significantly higher (86.67%,93.33%,92.86%,87.50% and 90% respectively) (Table 22).

Studies on topographic pattern of neuronal injury have shown that term infants with predominant injury to basal ganglia and thalamus have an unfavorable neurological outcome [77, 78, 79] . Rutherford et al compared MRI and cranial ultrasound findings with outcome at 1 year of age and found a poor outcome, if both the investigations showed abnormality in basal ganglia or thalamus [78] . Mercuri et al [79] reported that discrete lesions in basal ganglia were associated with normal motor outcome at 1 year of age in 57% cases, but Barnett et al followed up seven cases of asphyxia with similar lesions until school age and reported that only one of them had a completely normal motor outcome [80] . Barkovich et al have found basal ganglia watershed score to be an excellent predictor of the neurological outcome [51,53,55,56] . In our study it was seen that all infants with lesions in the basal ganglia and/ or thalamus had an abnormal outcome, which is consistent with the findings in other studies.

On combining EEG and CT the neurodevelopment can be predicted with a sensitivity of 100%, specificity of 33.33%, PPV of 60%, NPV of 100% and accuracy of 66.62%(p-0.042)(Table 23) . While combined result of EEG with MRI brain (4 dead cases assumed as having abnormal MRI) is 100% sensitive,40% specific, with 62.5% PPV ,100% NPV and 70% accurate(p-0.017)(Table 23). Hence it can be concluded that an EEG with MRI brain has maximum value in predicting the neurodevelopment at one year.

Conclusion

In a term newborn with hypoxic ischemic encephalopathy

1) A normal EEG and/ or CT scan of brain during the acute phase of illness is associated with good neurological outcome (100% sensitivity and 100% negative predictive value)
2) Burst suppression pattern in the EEG during the acute phase of illness is associated with a poor neurological outcome ($p < 0.001$)
3) Involvement of the basal ganglia or thalamus in the MRI at three months of age indicates a poor prognosis (p 0.002).
4) EEG combined with an MRI is most useful in predicting the neurological outcome(sensitivity 100%, negative predictive value 100%, accuracy 70%,positive predictive value 62.5% and p value 0.017)

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Annexure

Proforma

Case No:

Name:

Address:

Phone Number:

Date of Birth:

IP/OP No.

Gestational Age:

Birth Weight:

In Born/Out Born:

Obstetric Details and Problems G _ P _ L _ A _ :

Signs of fetal distress: Yes/ No _____

Mode of delivery: NRL/ Instrumental/ LSCS:

Indication: _____

Apgar score at 1 min: 5 min:

Details of resuscitation:_____

Positive Pressure Ventilation > 1 min: Y/N

_____

Sarnat score: stage 1/2/3:

Neonatal Seizures: Yes/No. Type _____

Anti epileptics required:_____

Control by _____ day/ uncontrolled

Discharge anti epileptics: _____

EEG Pattern: Normal continuous activity/ isolated temporal spikes/ transient discontinuous activity/ permanent discontinuous activity or suppression burst

CT: Normal/edema/others:

Details_____

MRI: 0/1/2/3/4 W/BG score

Seizure recurrence: No/Yes._____

Neuro assessment at 3 months _____

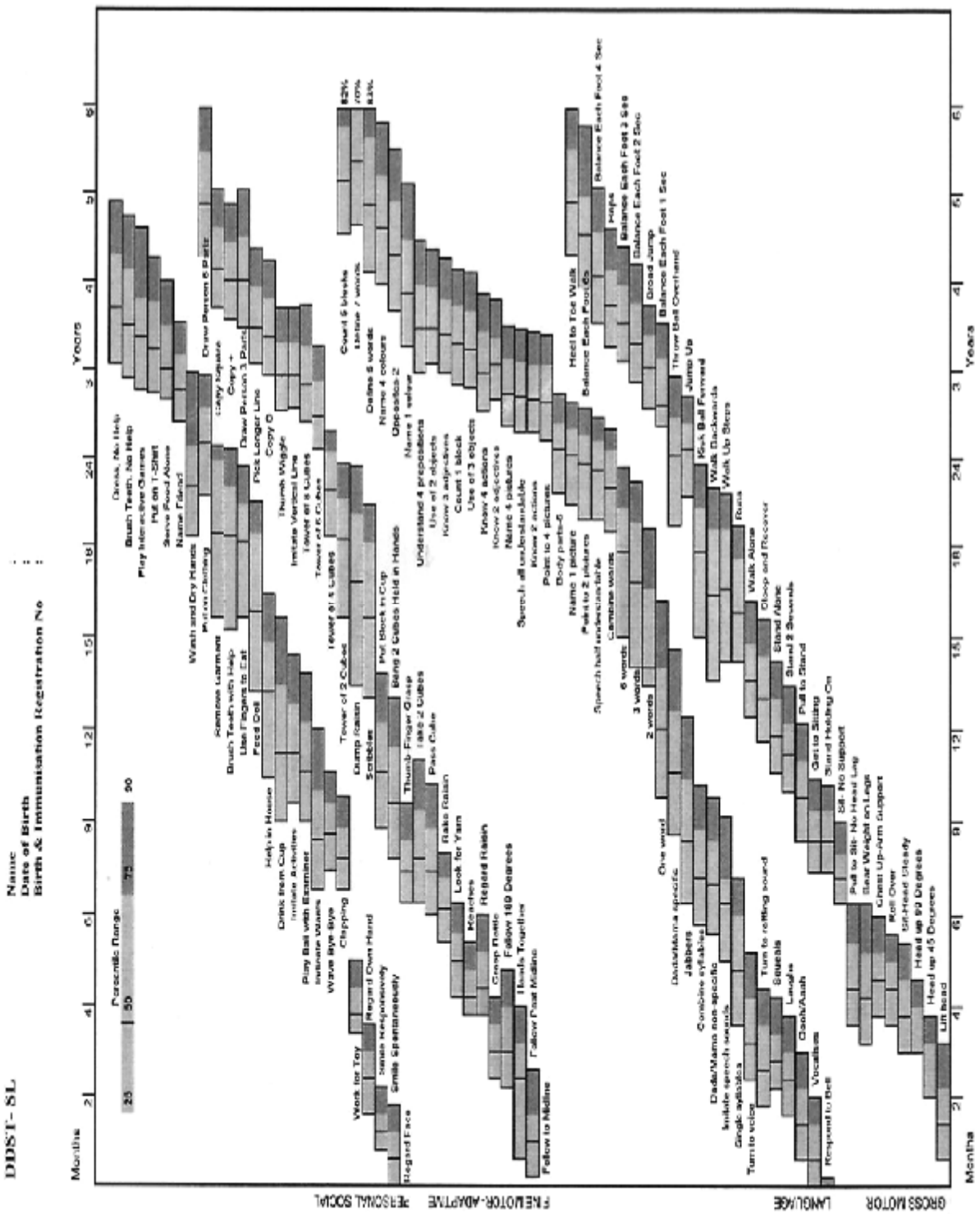
at 6 months _____

at 12 months_____

Normal/Abnormal

DDST2: Normal/Suspect/Untestable

DDST 2


DDST-SL
Name
Date of Birth
Birth & Immunization Registration No
Months
Years
Percentile Range
25
50
75
90
PERSONAL SOCIAL
FINE MOTOR-ADAPTIVE
LANGUAGE
GROSS MOTOR
Works for Toy
Regard Own Hand
Smile Responsively
Smile Spontaneously
Regard Face
Helpless Horse
Drink from Cup
Initiate Activities
Play Ball with Examiner
Imitate Vocals
Wave Bye-Bye
Clapping
Regard Raisin
Reach
Look for Yarn
Rake Raisin
Pass Cube
Thumb Finger Grasp
Take 2 Cubes
Dump Raisin
Scribble
Tower of 2 Cubes
Put Block in Cup
Bang 2 Cubes Held in Hands
Transfer Cube
Tower of 3 Cubes
Imitate Vertical Line
Thumb Wiggle
Copy O
Pick Longer Line
Draw Person 3 Parts
Copy +
Copy Square
Draw Person 6 Parts
Feed Self
Use Fingers to Eat
Remove Garment
Brush Teeth, w/o Help
Wash and Dry Hands
Name Friend
Serve Food Alone
Put on T-Shirt
Play Interactive Games
Brush Teeth, No Help
Follow Past Midline
Hands Together
Follow 180 Degrees
Grasp Pellet
Imitate Scribble
Tower of 6 Cubes
Tower of 8 Cubes
Imitate Circular Scribble
Copy Vertical Line
Copy Horizontal Line
Copy Circle
Copy Cross
Copy Square
Draw Person 3 Parts
Draw Person 6 Parts
Point to 4 Pictures
Name 1 Picture
Point to 2 Pictures
Speech half understandable
Name 4 Pictures
Know 2 Actions
Know 2 Adjectives
Know 4 Actions
Use of 3 Objects
Count 1 Block
Know 3 Adjectives
Use of 2 Objects
Understand 4 Prepositions
Name 1 Color
Count 6 Blocks
Define 5 Words
Name 4 Colors
Opposites 2
Use 7 Words
Use 5 Words
Use 3 Words
2 Words
3 Words
6 Words
Combine Words
One Word
Babbles
Dada/Mama non-specific
Combine Syllables
Imitate Speech Sounds
Single Syllables
Turns to Voice
Turn to Rattling Sound
Squeals
Laughs
Coos/Aahs
Vocalizes
Respond to Bell
Head up 45 Degrees
Head up 90 Degrees
Sit-Head Steady
Roll Over
Chest Up-Arm Support
Bear Weight on Legs
Pull to Sit- No Head Lag
Sit- No Support
Stand Holding On
Gets to Sitting
Pull to Stand
Stand 2 Seconds
Stand Alone
Creep and Recover
Walk Alone
Runs
Walk Up Stairs
Walk Backwards
Kick Ball Forward
Jump Up
Throw Ball Overhand
Broad Jump
Balance Each Foot 1 Sec
Balance Each Foot 2 Sec
Balance Each Foot 3 Sec
Hops
Balance Each Foot 4 Sec
Heel to Toe Walk
Balance Each Foot 6s
Lift Head
Follow to Midline
Regard Face
Smile Spontaneously
Regard Own Hand
Senses Hand Regard
Regard Raisin
Reach
Grasp Pellet
Follow 180 Degrees
Hands Together
Follow Past Midline
Transfer Cube
Pass Cube
Take 2 Cubes
Bang 2 Cubes Held in Hands
Thumb Finger Grasp
Pick Up Raisin
Pick Up Pellet
Pick Up Cube
Pull Block in Cup
Tower of 2 Cubes
Dump Raisin
Scribble
Tower of 3 Cubes
Tower of 6 Cubes
Tower of 8 Cubes
Imitate Vertical Line
Thumb Wiggle
Copy O
Pick Longer Line
Draw Person 3 Parts
Copy +
Copy Square
Draw Person 6 Parts
Feed Self
Use Fingers to Eat
Remove Garment
Brush Teeth, w/o Help
Wash and Dry Hands
Name Friend
Serve Food Alone
Put on T-Shirt
Play Interactive Games
Brush Teeth, No Help
Follow Past Midline
Hands Together
Follow 180 Degrees
Grasp Pellet
Imitate Scribble
Tower of 6 Cubes
Tower of 8 Cubes
Imitate Circular Scribble
Copy Vertical Line
Copy Horizontal Line
Copy Circle
Copy Cross
Copy Square
Draw Person 3 Parts
Draw Person 6 Parts
Point to 4 Pictures
Name 1 Picture
Point to 2 Pictures
Speech half understandable
Name 4 Pictures
Know 2 Actions
Know 2 Adjectives
Know 4 Actions
Use of 3 Objects
Count 1 Block
Know 3 Adjectives
Use of 2 Objects
Understand 4 Prepositions
Name 1 Color
Count 6 Blocks
Define 5 Words
Name 4 Colors
Opposites 2
Use 7 Words
Use 5 Words
Use 3 Words
2 Words
3 Words
6 Words
Combine Words
One Word
Babbles
Dada/Mama non-specific
Combine Syllables
Imitate Speech Sounds
Single Syllables
Turns to Voice
Turn to Rattling Sound
Squeals
Laughs
Coos/Aahs
Vocalizes
Respond to Bell
Head up 45 Degrees
Head up 90 Degrees
Sit-Head Steady
Roll Over
Chest Up-Arm Support
Bear Weight on Legs
Pull to Sit- No Head Lag
Sit- No Support
Stand Holding On
Gets to Sitting
Pull to Stand
Stand 2 Seconds
Stand Alone
Creep and Recover
Walk Alone
Runs
Walk Up Stairs
Walk Backwards
Kick Ball Forward
Jump Up
Throw Ball Overhand
Broad Jump
Balance Each Foot 1 Sec
Balance Each Foot 2 Sec
Balance Each Foot 3 Sec
Hops
Balance Each Foot 4 Sec
Heel to Toe Walk
Balance Each Foot 6s
Lift Head

Abbreviations

AAP-American Academy of Pediatrics

ACOG- American College of Obstetricians and Gynecologists

aEEG- amplitude integrated electroencephalogram

BG/W score- basal ganglia watershed score

CT- computed tomography

CytOX- cytochrome oxidase

DDST2- denver developmental screening test 2

EEG – electroencephalogram

FLP- follow up

HIE- hypoxic ischemic encephalopathy

ICU- intensive care unit

LSCS- lower segment cesarean section

MRI- magnetic resonance imaging

MRS- magnetic resonance spectroscopy

NA-not available

NIRS- near infra red spectroscopy

NOS- nitrogen oxide synthase

NPV- negative predictive value

OPD-out patient department

PET- positron emission tomography

PPV- positive predictive value

ROS- reactive oxygen species

VEP- visual evoked potential

sl no	name	sex	DOB	BW	GA	inborn/outborn	order of birth	fetal distress	mode of delivery
1	b/o bagyalakshmi	0	15/6/10	1	2	1	0	0	0
2	b/o aajara	0	21/3/10	2	1	1	0	1	2
3	b/o sathya	1	18/11/09	1	0	1	0	1	1
4	b/o leelavathi	0	20/10/10	1	2	0	0	3	2
5	b/o revathy	0	11/6/2010	1	3	1	0	0	0
6	b/o anitha	1	14/10//10	1	1	0	0	1	0
7	b/o kavitha	0	1/9/2010	1	3	1	0	1	2
8	b/o jothimani	0	31/10/09	1	2	1	0	0	0
9	b/o annapoorani	0	28/9/09	1	2	1	0	1	1
10	b/o deepa	0	14/6/10	3	3	0	0	1	1
11	b/o lakshmi	0	31/5/10	3	3	1	0	1	2
12	b/o sathya ramasamy	0	25/9/09	1	1	1	0	1	2
13	b/o ambika	0	24/6/10	0	0	0	1	0	0
14	b/o priya	1	19/4/10	2	1	1	0	1	2
15	b/o thangammal	0	23/6/10	1	2	1	0	2	2
16	b/o ganapriya	0	22/7/10	3	2	1	0	0	0
17	b/o bhuvaneshwari	0	14/10/10	1	1	1	0	1	1
18	b/o sowmya	0	11/6/2010	1	2	1	0	0	0
19	b/o nirmala	0	22/5/10	1	1	1	0	0	2
20	b/o menaka	0	25/4/10	2	1	0	0	1	1
21	b/o priyadarshini	0	18/7/10	2	2	0	1	1	2
22	b/o malarvizhi	0	8/6/2010	1	1	0	0	0	2
23	b/o jeeva	1	23/11/10	1	2	1	0	1	1
24	b/o sudha	0	21/6/10	2	2	0	1	3	1
25	b/o suganya	0	12/3/2010	2	3	1	0	1	1
26	b/o shalini	0	20/6/09	2	2	1	0	3	1
sl no	name	sex	DOB	BW	GA	inborn/outborn	order of birth	fetal distress	mode of delivery
27	b/o sumathy	0	11/9/2009	2	3	1	1	1	2
28	b/o rajeshwari	1	9/1/2010	1	2	0	0	1	1
29	b/o annapoorani	0	29/6/09	1	0	1	0	1	2
30	b/o manjula	1	17/4/10	2	3	0	1	1	1
31	b/o santhanalakshmi	1	8/8/2009	1	2	1	0	1	2

indication	apgar @1	apgar @2	resuscitation	sarnat stage	seizures	type of seizure	antiepileptic drug	seizure control	discharge anti-epileptic
	3	5	0	1	0	4	1	1	1
2	3	4	0	3	0	2	1	2	1
0			0	2	0	4	0	1	1
2	3	5	0	2	0	1	1	1	1
	2	5	0	2	0	2	1	1	1
	3	7	0	3	0	3	1	2	1
0			0	2	0	4	1	2	1
	4	5	0	1	0	3	0	0	1
0	3	6	0	3	0	4	1	2	1
2	4	7	0	1	0	3	0	1	1
0	3	5	0	2	0	2	1	1	1
2	4	6	0	2	0	3	1	3	1
	3	4	0	3	0	2	1	2	1
0	3	6	0	2	0	2	1	2	1
0			0	2	0	4	1	2	1
	4	5	0	2	0	1	1	1	1
0			0	2	0	3	0	0	1
	3	5	0	1	0	3	1	1	1
1	4	5	0	2	0	3	1	1	1
2	3	6	0	3	0	4	1	3	1
2	4	7	0	1	0	1	0	0	1
1	3	5	0	2	0	3	1	0	1
0	4	6	0	3	0	4	1	2	1
0	3	5	0	2	0	4	1	2	1
2	4	7	0	1	0	3	1	0	1
2	3	6	0	3	0	2	1	2	1
indication	apgar @1	apgar @2	resuscitation	sarnat stage	seizures	type of seizure	antiepileptic drug	seizure control	discharge anti-epileptic
0	4	6	0	3	0	2	1	3	2
0	3	7	0	1	0	3	0	0	1
2			0	3	0	4	1	2	1
0	3	8	0	1	0	3	0	0	1
0	4	8	0	1	0	3	0	0	1

eeg pattern	ct	mri	seizure recurrence	neuro assessment at 12months	DDST 2	outcome
2	0	0	0	0	1	1
3	2	3	0	1	2	2
0	0	0	0	0	1	1
3	2	2	0	1	2	2
2	0	0	0	0	1	1
2	1	0	0	0	2	2
1	0	0	0	0	1	1
2	0	0	0	0	1	1
3	1	1	0	1	2	2
0	0	0	0	0	1	1
3	1	na	na	na	na	0
2	1	0	0	0	2	2
3	1	na	1	na	na	0
3	2	3	1	1	2	2
3	1	na	na	na	na	0
1	0	2	0	0	1	1
1	0	0	0	0	1	1
0	0	0	0	0	1	1
3	1	1	0	1	2	2
3	1	na	1	na	na	0
0	0	0	0	0	1	1
0	0	0	0	0	1	1
3	1	3	0	1	2	2
3	1	3	0	1	2	2
2	0	0	0	0	1	1
3	1	3	1	1	2	2
eeg pattern	ct	mri	seizure recurrence	neuro assessment at 12months	DDST 2	outcome
3	2	no flp	no flp	no flp	nolp f	no flp
1	0	0	0	0	1	1
3	2	3	1	1	2	2
2	0	0	0	0	1	1
0	1	0	0	0	1	1

Key to Master Chart

Name

Sex: male 0, female 1

Birth weight:

1) 2-2.5 **à** 0
2) 2.5-3 **à** 1
3) 3-3.5 **à** 2
4) >3.5 **à** 3

Gestational age(GA)

1) 37-38weeks **à** 0
2) 38-39weeks **à** 1
3) 39-40weeks **à** 2
4) 40-41 **à** 3
5) 41-42 **à** 4

Inborn/outborn

1) Inborn 0
2) Outborn 1

Order of birth

1) 1st **à** 0
2) 2nd **à** 1
3) 3rd **à** 2
4) 4th **à** 3

Mode of delivery

1) Normal delivery **à** 0
2) Instrumental **à** 1

3) Lscs **à** 2

Indication

1) Fetal **à** 0
2) Maternal **à** 1
3) Both **à** 2

Fetal distress

1) No distress **à** 0
2) Fetal bradycardia **à** 1
3) Msaf **à** 2
4) Abnormal ctg **à** 3

Resuscitation

1) No PPV **à** 0
2) PPV **à** 1

Sarnat stage **à** 1,2 and 3

Seizure

1) Yes **à** 0
2) No **à** 1

Type of seizure

1) Subtle **à** 0
2) Focal **à** 1
3) Generalized **à** 2
4) Myoclonic **à** 3

Antiepileptics

1) Single drug **à** 0
2) ≥2 **à** 1

Seizure control

1) <24hrs **à** 0
2) >24-72 hrs **à** 1
3) 4-7days **à** 2
4) >7/uncontrolled **à** 3

Discharge antiepileptic

1) Nil **à** 0
2) Single **à** 1
3) >1 **à** 2

Eeg pattern

1) Normal continuous activity
2) Isolated temporal spikes
3) Transient discontinuous activity
4) Permanent discontinuous activity/suppression burst

CT

1) Nl **à** 0
2) Oedema **à** 1
3) Others **à** 2

MRI

Basalganglia/watershed score	
0	Normal
1	Abnormal signal in basal ganglia or thalamus
2	Abnormal signal in cortex
3	Abnormal signal in cortex and basal nuclei (basal ganglia or thalami)
4	Abnormal signal in entire cortex and basal nuclei

Seizure recurrence

1) No **à** 0
2) Yes **à** 1

Neuro assessment

1) Nl **à** 0
2) Deficits **à** 1

DDST2

1) normal **à** 0 **à** 1
2) suspect **à** 1 **à** 2
3) untestable **à** 2 **à** 3

Outcome

1) Death **à** 0
2) Normal **à** 1
3) Abnormal **à** 2